REMARKS

Prior to entry of the present amendment, claims 21-30 are pending. Claims 28 and 29, due to a Restriction Requirement, have been withdrawn. Claim 26 is rejected under 35 U.S.C. § 112, second paragraph, claims 21-27 and 30 are rejected under 35 U.S.C. § 112, first paragraph, and claim 21 is objected to on formal grounds. Applicants address each basis for rejection as follows.

Claim amendments

Claims 22-27 have been cancelled.

Claim 21 has been amended to delete the recitation of the phrases "curing or prevention" and "a DNA sequence encoding a Gas6 compound."

Claim 21 has been further amended to specify particular types of "erythropoietin" (EPO) and "Gas6 compounds" recited in the specification as filed.

Support for naturally occurring erythropoeitin is found, for example, at page 12, lines 14-16, of the WO 2005/007183 publication, where the specification states:

> Erythropoeitin or Epo as used herein refers to the naturally occurring human cytokine, produced primarily in the kidney which stimulates the production of red blood cells.

Support for glycosylation variants of erythropoeitin is found, for example, at page 12, lines 18-21, of the WO 2005/007183 publication. Here the specification states:

> Well described erythropoietin analogues are the hyperglycosylated recombinant proteins epoetin and darbepoetin (or novel erythropoiesis stimulating protein, NESP), of which the structures differ from naturally occurring Epo only by the number of N-linked oligosaccharide on the protein.

And at page 13, lines 3-4, where the specification states:

> US patent application 2003/0077753 describes EPO variants with modified glycosylation patterns.

Support for point mutants and deletion mutants is found, for example, at page 12, lines 24-28, of the WO 2005/007183 publication, where the specification states:

> The expression product of deletion mutants of a synthetic human Epo cDNA, wherein the point mutations and small deletions in helices and interhelical regions of the four alpha helical bundle motif have been shown to display biological activity (Bittorf et al. (1993) FEBS Lett **336**, 133-136; Boissel et al. (1993) J. Biol. Chem. **268**, 15983-15993).

Fragments of Gas6 lacking the A domain or a fragment of Gas6 consisting essentially of the D domain, find support, for example, at page 11, lines 11-14, of the WO 2005/007183 publication. Here the specification states:

> [F]ragments of Gas6 which lack the A domain as well as fragments which consist essentially of the D domain, such as those described in WO 96/28548. The sequence identity of such variant Gas6 proteins can be 70% or greater compared to the wildtype Gas6.

Gas 6 mutants are described, for example, at page 11, lines 3-7, of the WO 2005/007183 publication, where the specification states:

> As used herein "mutants of Gas6" refers to modified Gas6 proteins of equal length as wild type Gas6 but with one or more modified amino acids. The sequence homology of such modified Gas6 proteins have a homology of 95% or greater, or 98% or greater or 99% or greater compared to the wildtype Gas6.

In addition, "Gas 6 function" is described, for example, at page 11, lines 15-23, of the WO 2005/007183 publication. Here the specification states:

> A Gas6 analogue as used herein refers to a molecule capable of activating the Tyr, Mer and/or Axl receptor on hematopoietic cells, in a similar way as Gas6. These molecules can optionally be directly or indirectly derived from Gas6 ... Gas6 analogues can be screened by evaluating the activation of a Gas6 receptor by assaying for example the tyrosine kinase activity of such receptor on a substrate peptide.

New claims 31 and 32 have been added. Claim 31 recites particular glycosylation variants. Support for this claim is found, for example, at page 12, lines 18-21, of the WO 2005/007183 publication. Here the specification states:

> Well described erythropoietin analogues are the hyperglycosylated recombinant proteins epoetin and darbepoetin (or novel erythropoiesis stimulating protein, NESP), of which the structures differ from naturally occurring Epo only by the number of N-linked oligosaccharide on the protein.

Claim 32 recites a particular condition, namely "anemia caused by or associated with chronic renal failure." Claim 32 finds support, for example, at page 14, lines 2-3, of the WO 2005/007183 publication.

No new matter has been added by the present amendments. Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Objection to the Claims

Claim 21 is objected to for not being directed to the elected invention. Claim 21, as amended, is directed to the administration of proteins and no longer recites administration of a DNA sequence. This basis for objection may be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 26 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite in reciting a term that lacks antecedent basis in the claim from which claim 26 depends. Claim 26 has been cancelled and, therefore, this basis for rejection is moot.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 21-27 and 30 are rejected under 35 U.S.C. § 112, first paragraph for an asserted lack of enablement and written description in the specification as filed. Applicants address these bases for rejection below.

Enablement

The Office sets forth six reasons for the enablement rejection of claims 21-27 and 30. Each reason is addressed as follows.

Reason 1

The Office asserts that the specification is not enabling for "curing" and "preventing" because these "are not relative terms, it is total." The claims as amended are directed to methods of treatment and no longer recite curing or prevention. This basis for the enablement rejection may be withdrawn.

Reason 2

The Office rejects claim 21 and its dependent claims based on the assertion the "specification fails to teach a synergistic rescue effect on erythropoiesis." In particular, the Office states (page 5):

> A synergistic effect of increased hematocrit levels was see, **but this effect was only seen when recombinant Gas6 protein and recombinant EPO protein was administered to Gas6-/- knockout mice treated with PHZ to induce anemia** ... The general patient populations would not have a knockout for the Gas6 gene. (Emphasis original.)

Applicants respectfully disagree with the Office's statements.

Applicants refer to Example 11 of the specification where a transgenic mouse is used which has stable chronic anemia due to deficiency of erythropoeitin. In these experiments heterozygotic mice are used which are "moderately anemic with hematocrit levels below 45% but higher than 25%. Homozygous mice display hematocrit levels comparable to those observed in patients with chronic renal failure." The experimental results described in Example 11 demonstrate that "*[t]he synergistic benefical effect became significant* when low dose rGas6 (2 microgram per day) was administered together with Epo (10 IU per day), resulting in a rise in the hematocrit higher than Epo alone or rGas6 alone. Thus, Gas6 is effective in chronic anemia, augments the effects of Epo, and may have Epo dose-sparing effects" (page 32, lines 16-21, of the WO 2005/007183 publication; emphasis added).

Accordingly, synergistic effects have been demonstrated in two models, namely in a $Gas6^{-/-}$ model, as correctly indicated by the Office, ***and*** in a heterozygous erythropoietin deficient model. Both models are representative for anemic patients, either by Gas6 deficiency, which is a model for an inadequate erythropoietin response,

or by the erythropoeitin deficient mouse model (134.3 LC, Epo-TAg(H)) as described in Example 11.

The models used in obtaining the results described in the present specification are art-recognized as valid models for anemia. In support of this assertion, Applicants direct the Office's attention to the following exemplary scientific literature:

1) The data disclosed in the present invention using the gas6-/- model have been published in a peer-reviewed journal, indicating that the relevant scientific community recognizes the Gas6 knockout model as a valid model for anemia (Angelillo-Scherrer et al., "Role of Gas6 in erythropoiesis and anemia in mice," J. Clin. Invest. **118**, 583-596, 2008; copy of abstract enclosed as Exhibit 1). The abstract states:

> In a transgenic mouse model of chronic anemia caused by insufficient Epo production, Gas6 synergized with Epo in restoring hematocrit levels.

2) The 134.3LC model (Epo-Tag(H)) used in obtaining the results described in Example 11 of the specification has been described by at least two independent groups as a valid model for anemia, as indicated by the abstracts of the following publications (copies enclosed as Exhibits 2-5):

Macarlupú et al., "Time course of ventilatory acclimatisation to hypoxia in a model of anemic transgenic mice," Respir. Physiol. Neurobiol. **153**:14-22, 2006, which states:

> Thus, the objective of our study was to determine if *anemic Epo-TAg(h)* mice could survive in hypoxia despite low oxygen carrying capacity. (Emphasis added.)

Macarlupú et al., "Characterization of the ventilatory response to hypoxia in a model of transgenic anemic mice," Respir. Physiol. Neurobiol. **150**:19-26, 2006, which states:

> The objective of this study was to characterise the ventilation pattern at different inspired oxygen fraction in a *model of chronic anemic mice [Epo-TAg(h)]*. (Emphasis added.)

Binley et al., "Long-term reversal of chronic anemia using a hypoxia-regulated erythropoietin gene therapy," Blood **100**:2406-2413, 2002, which states:

> Homozygous Epo-TAg(h) mice display cardiac hypertrophy, a common adaptive response in patients with chronic anemia ... We conclude that the OBHRE [Oxford Biomedica hypoxia response element] promoter gives rise to

> physiologically regulated Epo secretion such that the hematocrit level is corrected to healthy in *anemic Epo-TAg(h) mice*. (Emphasis added.)

Rinsch et al., "Delivery of erythropoietin by encapsulated myoblasts in a genetic model of severe anemia," Kidney Int. **62**:1395-1401, 2002, which states:

> The transgenic mouse strain 134.3LC (Epo-TAg(H)) displays a severe chronic anemia resembling that observed clinically during CRF [chronic renal failure], while displaying an active, normal life span.

Applicants submit that the above-cited publications provide additional support that the models used to obtain the experimental results described in the specification are representative for evaluating the effect of pharmaceutically active compounds on anemia. This basis for the enablement rejection may also be withdrawn.

Reason 3

The Office asserts that "[t]he specification fails to demonstrate that anemia has been treated," that the examples only refer to the measurement of hematocrit levels, and that "[t]he instant specification has not established that hematocrit levels are tantamount to erythropoiesis levels." Applicants respectfully disagree with the Office's characterization of the specification.

Applicants direct the Office's attention to page 28, lines 19-21, of the WO 2005/007183 publication, which describe *reticulocyte indexes, which are indicative of erythropoeisis levels*. While the Office appears to point to the experiments measuring hematocrit levels summarized in Figures 4A and 4B, the reticulocyte indexes are distinct from the hematocrit levels.

In view of the above Applicants submit that the examples, in describing reticulocyte index results, indeed show that anemia has been treated.

Reasons 4 and 5

Applicants submit that the rejection of claims 23-26 for an asserted lack of enablement has been rendered moot by the cancellation of claims 23-26.

Reason 6

The Office asserts that the specification is not enabling for "analogues, mutants, variants or derivatives of Gas6 compounds, Gas6 protein or EPO protein." Claim 21 has been amended to recite particular glycosylation variants, point mutations, and deletion mutants of Gas6 or erythropoietin which, as taught in the sections of the specification cited above, were known in the art at the time of filing. In addition, Applicants' specification provides the necessary functional criteria (namely stimulation the production of red blood cells) to assess whether or not a given variant of mutation of erythropoietin is encompassed by the present claims. Similarly, as described above, the specification describes that Gas6 function can be determined by binding to one of its receptors, Axl, Sky, and Mer. In view of the extensive teachings in Applicants' specification and the knowledge in the art, Applicants submit that one skilled in the art would know how to make and use, in the claimed methods, the Gas6 and erythropoietin proteins recited in the claims absent undue experimentation using nothing more than standard techniques.

For all the above reasons, Applicants submit that the claims, as amended, are free of all bases for the enablement rejection.

Written Description

Claims 21-27 and 30 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. As noted above, claim 21 has been amended to recite particular Gas6 compounds and erythropoietin proteins described in the specification as filed. Clearly, in view of the teachings of the specification, one skilled in the art would recognize that Applicants were in possession of the glycosylation variants, point mutations, and deletion mutants of erythropoietin and Gas6 encompassed by claim 21, as amended, and its dependent claims at the time of filing. Applicants submit that the present claims are free of the written description rejection. This basis for the rejection under 35 U.S.C. § 112, first paragraph may also be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for two (2) months, to and including February 12, 2009, and payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 10 February 2009

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